Screening Solvent Effects in Anion Recognition

Chem - Preview

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In this issue of Chem, Flood and co-workers examine solvent effects on chloride anion binding within a neutral macrocyclic host.*[1] *An inverse relationship between the complexation energies and the dielectric constants of aprotic solvents was found, revealing the limit at which electrostatic interactions are no longer the dominant contributors to binding.

Significant progress has been made using empirical approaches to gain a quantitative understanding of molecular recognition processes involving neutral species.[2] However, corresponding knowledge of interactions involving charged species remains underdeveloped. Despite substantial progress, both in terms of the computational power and theoretical methods available, direct computational prediction of molecular recognition processes occurring in solution remains highly challenging. Thus, the advancement of our understanding of molecular recognition phenomenon still relies heavily on empirical investigations. One powerful empirical approach for dissecting the underlying physicochemical origins of molecular recognition is to perform a solvent screen, in which solvent properties such as polarisability, solvophobicity and hydrogen-bonding donor and acceptor constants are systematically varied.[3,4] However, even with neutral species it can be difficult to find suitable supramolecular model systems that enable solvent screening and the determination of reliable quantitative experimental data. The situation becomes even more difficult when charges are involved, as the solubility of the components of the system may vary wildly between different solvents, while counterion effects, conformational flexibility and preferential solvation can further complicate any attempted analysis. Accordingly, investigations of anion recognition in which more than a handful of solvents have been examined are rare,[5-7] and an empirical scale describing the binding abilities of anions was only very recently established.[8] The limited understanding of the relative importance of potential energetic contributors to anion recognition undoubtedly impedes the design of new synthetic receptors that could be exploited in industrially important separations, sensing, medicine, membrane transport, templated synthesis, catalysis and beyond.[9]

In the present issue, Flood and co-workers report measurements of the binding of chloride anions to neutral triazolophane macrocycles (Figure 1A) and a phenomenological deconvolution of the observed solvent effects (Figure 1B). UV-Vis and NMR titrations were used to determine the 1:1 binding constants of macrocycle▪Cl^- complexes in several solvents and solvent mixtures, from apolar solvents such as chloroform and dichloromethane to polar solvent mixtures such as 10% (w/w) water in dimethylsulfoxide. These solvent screening experiments were key to revealing the underlying physicochemical origins of the anion recognition process. The experimental binding data were correlated against numerous parameters that have been used to describe solvent properties including dielectric constant (ε_r), bulk polarisability (P), surface tension (γ), cohesive energy density (ced) and hydrogen bond donor (a) and acceptor constants (β).[2,3,4] Correlations with any of these individual properties gave correlation coefficients no better than $R^2 = 0.77$ even when aprotic solvents were only included in the correlations. In contrast, a correlation coefficient of $R^2 = 0.93$ was found for the same data when plotted against the inverse of the dielectric constant ($1/\varepsilon_r$) for solvents spanning from $\varepsilon_r = 4.7$ (chloroform) to 46.8 (dimethylsulfoxide), as shown on the left-hand side of Figure 1B. This correlation with the inverse dielectric constant strongly indicates that the trends in the interaction energies are dominated by electrostatic interactions. Indeed, it might have been expected that the multiple $CH\cdots Cl^-$ interactions present in the triazolophane▪Cl^- complex (Figure 1A) should be dominated by electrostatics in apolar solvents, as was also confirmed to be the case in gas-phase calculations. The

more interesting aspect of the experimental data occurs in the more polar solvents where the dielectric effect seen in Figure 1B begins to level off. SAPT calculations were performed on the anion-bound complex that allowed the total interaction energy to be dissected into electrostatic, exchange (repulsion), induction (polarisation) and dispersion components. These computations support Flood's assertion that anion binding is governed by residual van der Waals and inductive polarisation in polar solvents that largely cancel out the otherwise dominant electrostatic interactions (e.g. in acetonitrile and dimethylsulfoxide). Moreover, the authors used the observed empirical relationship with the inverse of the dielectric constant combined with computed binding energies to accurately predict the experimental binding constants of the macrocycle▪Cl^- complexes in 1,2-dichloroethane and water-saturated nitrobenzene (experimental data shown as blue circles in Figure 1B).

The correlation of the complexation energies with the inverse dielectric constant is interesting given that the dielectric constant is a property of bulk solvent that may not necessarily be manifested on the nanoscale. Indeed, local interactions such as hydrogen bonds may result in preferential solvation of complementary hydrogen bonding sites rather than the continuum averaging of solvent properties that is observed in macroscopic bulk solution. Calculations supported the suggestion that the experimental trend observed in Figure 1B arose from the triazolophane cavity being too small to bind most of the solvents examined, thus reducing the ability of those solvents to compete with anion binding. Consistent with this hypothesis, the addition of water to dimethylsulfoxide, which is small enough to solvate the inner cavity of the macrocycle, was found to further dampen anion binding (preferential binding regime on the right of Figure 1B).

The finding that the binding energies correlated with the inverse of the dielectric constant opens the possibility that explicit solvent models that treat the solvent as a continuous field may prove to be useful in modelling other recognition events occurring on the molecular level, but more work is required to see if this is indeed the case beyond simple chloride binding. Such a possibility is promising since implicit, continuum solvent models are much easier to implement than explicit models that place discrete solvent molecules around a solute. While explicit solvent models are rigorous, they are extremely computationally expensive to implement; even when sufficient computational power is available, modelling may only cover a few picoseconds and the certainty associated with energetic estimates can be larger than the magnitude of a particular interaction of interest. Accordingly, the work of Flood and co-workers highlights the importance of pairing experimental and theoretical approaches as we seek to unravel the physicochemical origins of recognition processes occurring on the molecular level in solution.

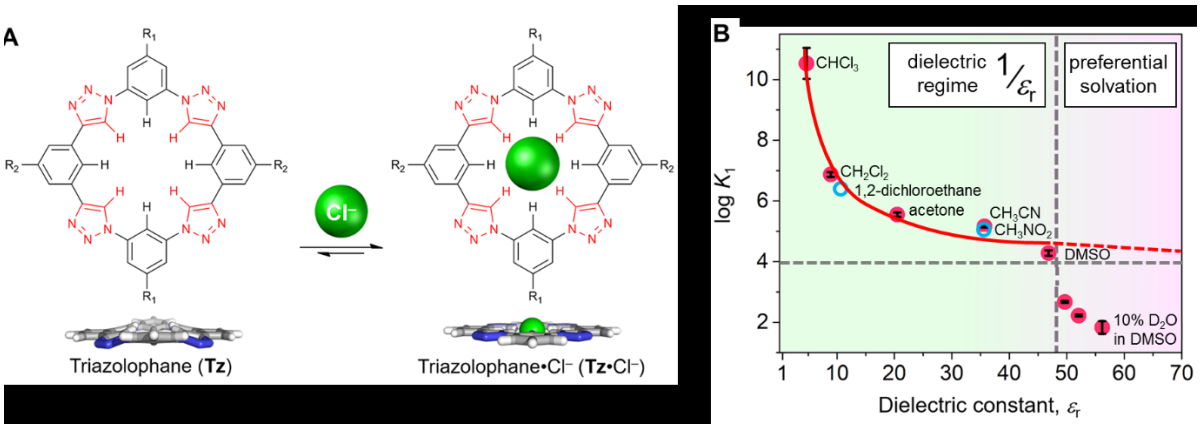

Figure 1. (**A**) Binding equilibrium for chloride with a neutral triazolophane host. (**B**) Dependency on the log of the association constant of binding (K_1) on the dielectric constant of the solvent (ε_r). Two binding regimes are observed; one in which electrostatic interactions dominate the energetic trends (left) and another in which preferential solvation of the macrocyclic binding site by water cancels out residual interactions arising from van der Waals forces and inductive polarisation (right). Blue circles represent experimental data that were initially predicted and subsequently shown to fit on the red correlation.

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